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Dated: August 21, 2003 Signature: Staci Harris
(Staci V. Harris)

Docket No.: HO-P02681US1
(PATENT)

#38
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8-28-03


**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Orla M. Conneely, et al.

Application No.: 09/058,589 Art Unit: 1617

Filed: April 10, 1998 Examiner: S. Wang

For: LACTOFERRIN AS REGULATOR OF ALLERGEN-INDUCED TUMOR NECROSIS FACTOR-ALPHA PRODUCTION AND THERAPEUTIC APPLICATIONS

MS Non-Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**1.132 DECLARATION**

Dear Sir:

The undersigned, Atul Varadhachary, M.D., Ph.D., hereby declares and states that:

1. My current position is a President and Chief Operating Officer at Agennix, Inc. I am skilled in the art of immunology, more specifically, the role that lactoferrin plays in the immune response. See attached curriculum vitae.

2. I have read the above-referenced application, and I have read the pertinent Office Action.

3. The present invention is drawn to the use of lactoferrin to prevent or treat an allergen-induced inflammatory response. The mechanisms involved in an allergen-induced immune response differs from an immune response resulting from an insult by a pathogenic agent, such as bacteria or viruses. Inflammation that occurs via a pathogenic agent is typically a result of endotoxin toxicity. Endotoxins are

toxins that are released from the pathogen. Thus, an endotoxin is not innocuous; it is toxic to the cell and triggers phagocytes to release cytokines that produce local or systemic symptoms. An allergen-induced inflammatory response results from the immune system responding to an innocuous agent, not a pathogenic agent.

4. The immune system is divided into nonspecific immunity (also known as innate immunity) and specific immunity (also known as adapative immunity). The term nonspecific implies that the immune mechanisms do not act on only one or two specific invadors, but rather provide a more general defense by simply acting against anything recognized as not self. The term specific immunity involves mechanisms that recognize specific threatening agents and respond by targeting their activity against these agents.

5. Most pathogens are detected and destroyed by mechanisms of innate immunity. The first line of defense of innate immunity is the surface epithelia that provides a physical barrier. If the epithelia is breached by the pathogen, the pathogen is then faced with the second line of defense of innate immunity, which is an alternative pathway of complement activation or phagocytosis. Attack by the alternative pathway of complement activation occurs spontaneously in plasma and opsonizes or destroys the pathogen while sparing the host cells. Alternatively, the pathogen can be directly recognized and engulfed by phagocytic macrophages or neutrophils. Macrophages and neutrophils have granules that contain enzymes, proteins and peptides that mediate an intracellular anti-bacterial response. Only if the pathogen breaches the first and second lines of innate immunity will an adaptive immune response or specific immunity response ensue with the generation of antigen-specific effector cells that specifically target the pathogen.

6. An allergen is defined as an innocuous agent or antigen, such as an environmental agent, that elicits an allergic reaction. Allergic reactions are also known as hypersensitivity reactions that can be mediated by antibodies or specific T cells. There are four types of hypersensitivity reactions. Types I-III reactions are anti-body mediated and are distinguished by the different types of antigens that are recognized by the different classes of antibodies involved. Type I responses are mediated by IgE, which induces mast-cell activation. Type II and III reactions are mediated by IgG, which involves complement-mediated phagocytosis. More specifically, type II reactions are directed against cell-surface or matrix antigens,

whereas type III reactions are directed against soluble antigens. Type IV reactions are T-cell mediated and can be further subdivided into three groups. In one group, the tissue damage is caused by the activation of macrophages by $T_H1$ cells, which causes an inflammatory response. The second groups causes tissue damage by the activation of eosinophilic inflammatory responses by $T_H2$ cells. In the third group, the damage is caused directly by cytotoxic T cells. T-cell mediated reactions evolves over the course of 24-72 hours, thus T-cell mediated reactions or type IV reactions are also known as delayed hypersensitivity reactions. The course of events that occur in a T-cell mediated local inflammatory reaction are as follows: the T-cells enter the site of the allergen penetration, recognize complexes on antigen-presenting cells, and release inflammatory cytokines that result in an increase in local blood vessel permeability, bringing plasma into the tissue and recruiting accessory cells to the site, thus causing swelling. It is believed that lactoferrin plays a role in type IV or delayed hypersensitivity reactions. Thus, the role that lactoferrin plays in type IV hypersensitivity reactions is completely different than the role it plays in the innate immune response to a pathogen.

7. Teng et al. (WO 92/21752) teaches the use of lactoferrin as a treatment for antibacterial and antiviral infections (see page 4, lines 21-30 and page 13, lines 1-5). Britigan et al. (Advances in Experimental Medicine and Biology, 357:143-146, 1994) also teaches the use of lactoferrin to treat bacterial infections via scavening free radicals that are produced by phagocytosis. In fact, Britigan et al. further suggests that lactoferrin may play a role in ameliorating LPS-induced toxicity (see page 151, last sentence of summary). JP 07-233086 also teaches the antimicrobial effects of lactoferrin. Thus, Teng et al., Britigan et al., and JP07233086A teach the antimicrobial activity of lactoferrin (lactoferrin's activity against a pathogen), however, none of the references teach or suggest the use of lactoferrin to treat an allergen-induced immune response (lactoferrin's activity against an innocuous agent).

8. De Lacharriere (US Patent 5,656,581) does not describe that lactoferrin is a TNF antagonist. The term "TNF α antagonists" is defined in functional terms, see column 3 lines 4-10 of the De Lacharriere patent. It is stated that "all substances capable of inhibiting the release and/or synthesis and/or receptor binding of ...TNF alpha" are considered "TNF α antagonists." Without teaching the structures of potential TNF α antagonists, no one in the art would know how to select a candidate from millions of natural and recombinant biological molecules in order to test for its

ability to inhibit TNF α production. Such a general statement in De Lacharriere cannot be fairly construed as providing a suggestion for one skilled in the art to select lactoferrin, and specifically, to test its ability to inhibit TNF α production in dermal cells, and to conduct the test under the particular condition that the mammal has been inflicted with an allergen.

9. Nuijens et al. (J Mammary Gland Biol Neoplasia. 3:285-295, 1996) reports that lactoferrin suppresses IL-1 and TNF-α release from monocytes in response to LPS from Gram-negative bacteria. See last paragraph at page 287 that is cited by the Examiner. Nuijens does not teach or suggest that lactoferrin suppresses IL-1 or TNF-α production from dermal cells in response to an allergen, which is mediated through an LPS independent pathway. As such, Nuijens et al. is not on point and adds nothing to the notion of using lactoferrin for treatment of dermal inflammation, and more specifically allergen-induced inflammation. Thus, Nuijens et al. address the use of lactoferrin to treat a bacterial infection not the use of lactoferrin to treat an allergen-induced immune response.

10. I assert that one of skill in the art would not have been able use the lactoferrin composition in Teng et al. in combination with the lactoferrin compositions described in combination with any of the cited references to develop the lactoferrin composition of the present invention to treat an allergen-induced inflammatory response. The references cited by the Examiner teach the use of lactoferrin to inhibit LPS toxicity, which LPS toxicity is not involved in an allergen induced response.

I declare that all statements made here of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 8/19/03

Atul Varadhachary

Atul Varadhachary, M.D., Ph.D.

# ATUL VARADHACHARY, M.D., PH.D.

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## PROFESSIONAL EXPERIENCE

**Since 2002:** **President & Chief Operating Officer,** Agennix, Inc., Houston

**2001 to 2002:** **Executive Vice President,** Agennix, Inc., Houston

- Design and direct all preclinical research and development
- Select and help design rhLF related clinical indications and trials
- Direct patent prosecution and manufacturing scale-up
- Help define and implement core strategy, licensing and business development

**Since 2002:** **Adjunct Professor of Management**
Jones Graduate School of Management, Rice University, Houston.

**Since 2003:** **Adjunct Professor,** Baylor College of Medicine, Houston.

**1994 to 2001:** **Senior Engagement Manager,** McKinsey & Co., Houston

Supported senior executives and management teams in strategic planning and execution in a broad range of industries and functional areas in North America, Europe and Asia.

**1998 - 1999:** **Founder,** Pratham Health, Bombay (since renamed Niramaya Health Foundation)

Designed and implemented a preventive, micronutrient-based health program for over 50,000 preschool slum children, at an annual cost of less than a dollar a child.

Took a year's leave of absence from McKinsey & Co. to work with Pratham, a non-profit educational organization in India (www.pratham.org). Leveraged Pratham's existing infrastructure and resources to create the health program in less than six months. The program and the health organization have continued to grow in reach and scope. Pratham was recently recognized as one of three most innovative and impactful development projects by the Global Development Network, sponsored by the World Bank and Government of Japan.

**1992 - 1994:** **Postdoctoral Fellow in Biochemistry,** Johns Hopkins School of Medicine, Baltimore

Investigated the glycosyl phosphatidyl inositol pathway for possible points of therapeutic intervention using the Trypanosoma brucei VSG model. Experienced with a broad variety of molecular biological, biochemical and biophysical tools and techniques.

## EDUCATION

**1992:** **Ph.D. in Physiology,** Johns Hopkins University School of Medicine, Baltimore

**1988:** **Certification by the E.C.F.M.G.**
(Educational Commission for Foreign Medical Graduates, Philadelphia)

**1987:** **M.D.,** University of Bombay, India

## APPOINTMENTS, AWARDS AND ACADEMIC HONORS

***Johns Hopkins School of Medicine:***

- 4.0/4.0 Grade Point Average
- Member, Medical School Council (1991-93), Johns Hopkins University
- Founding President, Johns Hopkins University Postdoctoral Association (1992-94)

***L.T.M. Medical College:***

- Winner, Competitive Examination in Physiology (1982)
- National Merit Scholarship (1982)
- Editor, College Magazine, L.T.M. Medical College (1983-84)
- General Secretary, L.T.M. Medical College Students' Association (1984-85)
- 2nd place award in Internal Medicine and Pediatrics (1985)

***Board Memberships:***

- Pratham USA, Houston. Member, Board of Directors.
- Niramaya Health Foundation, Mumbai, India. Member, Board of Directors

***Other:***

- "Making a Difference Award," Children's Hope Foundation, New York, September 2002
- Co-chair, Electronic Media Committee, AAPI (American Association of Physicians of Indian Origin), 1998-99

## SELECTED ABSTRACTS AND PUBLICATIONS

Atul Varadhachary and Rick Barsky. Development of Recombinant Human Lactoferrin as a Pharmaceutical Agent. *Proceedings of the Sixth International Conference on Lactoferrin*, 2003. (Invited).

Atul Varadhachary, Karel Petrak, Jeffrey S. Wolf, Bert W. O'Malley, Federica Pericle. Recombinant Human lactoferrin: a Novel Oral Anti-Cancer Drug. *Proceedings of the American Society of Clinical Oncology*, 2003.

Teresa G. Hayes, Gauri R. Varadhachary, Dori Smith, Dawn Hintz, Atul Varadhachary. Phase I/II Clinical Trial of Oral Recombinant Human Lactoferrin in the Treatment of Chemo Resistant Solid Tumors. *Proceedings of the American Society of Clinical Oncology*, 2003.

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Peter Glynn and Atul Varadhachary. Recombinant human lactoferrin: a novel agent for the treatment of allergic asthma. (Invited manuscript, in preparation).

Atul Varadhachary, Karel Petrak, Bert O'Malley, Jr., and Ernest Yankee. Intratumoral injection of human recombinant Lactoferrin inhibits the growth of human tumors implanted in athymic nude mice. *Proceedings of the American Society of Clinical Oncology*, 2002.

K. Guntupalli, G.R. Varadhachary, J. Desai, T. Doshi, A. Varadhachary. Tobacco Prevalence and Risk Factors – A Thousand-Child Survey from India. Proceedings of WATCH (World Assembly on Tobacco Counters Health), 2002.

Rukmini Banerji, Madhav Chavan, Paresh Vaish and Atul Varadhachary. A point of light in Mumbai. *McKinsey Quarterly*, 2001, No. 1:156-165.

Fann M, Davies AH, Varadhachary A, Kuroda T, Sevier C, Tsuchiya T, Maloney PC. Identification of two essential arginine residues in UhpT, the sugar phosphate antiporter of Escherichia coli. *J Membr Biol.* 1998, 164(2):187-195

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Book Chapter: Identification and reconstitution of anion exchange mechanisms in bacteria. Chapter in *Advances in Cell and Molecular Biology of Membranes and Organelles*, 1995.

## SELECTED PATENT APPLICATIONS

Atul Varadhachary, Karel Petrak, and Rick Barsky. Oral human lactoferrin in the treatment of malignant neoplasms and other hyperproliferative diseases.

Atul Varadhachary, Karel Petrak, Rick Barsky and Bert W. O'Malley, Jr. Intratumorally injected lactoferrin in the treatment of hyperproliferative diseases.

Atul Varadhachary, Richard Barsky and Ernest Yankee. Use of lactoferrin in prophylaxis against infection and/or inflammation in immuno-suppressed subjects.

Jose Engelmayer and Atul Varadhachary. Lactoferrin in the treatment of wounds.

Peter Glynn and Atul Varadhachary. Oral lactoferrin in the treatment of allergic respiratory disorders.

Atul Varadhachary and Federica Pericle. Lactoferrin as an agent in the prevention of organ transplant rejection and graft-versus-host-disease.

Atul Varadhachary, Peter Glynn, Yenyun Wang and Jose Engelmayer. Lactoferrin in the reduction of circulating cholesterol, vascular inflammation, atherosclerosis and cardiovascular disease.

Karel Petrak and Atul Varadhachary. Oral Lactoferrin in the treatment of sepsis.

The **12/23** rule states that gene segments of immunoglobulin or T-cell receptors can be joined only if one has a recognition signal sequence with a 12 base pair spacer, and the other has a 23 base pair spacer.

In the context of immunoglobulins, α is the type of heavy chain in IgA.

The **ABO blood group system** antigens are expressed on red blood cells. They are used for typing human blood for transfusion. If they do not express A or B antigens on their red blood cells, people naturally form antibodies that interact with them.

The removal of antibodies specific for one antigen from an antiserum to render it specific for another antigen or antigens is called **absorption**.

**α:β T-cell receptor**: see **T-cell receptor**.

**Accessory cells** in adaptive immunity are cells that aid in the response but do not directly mediate specific antigen recognition. They include phagocytes, mast cells, and NK cells, and are also known as **accessory effector cells**.

The **acquired immune deficiency syndrome (AIDS)** is a disease caused by infection with the human immunodeficiency virus (HIV). AIDS occurs when an infected patient has lost most of his or her CD4 T cells, so that infections with opportunistic pathogens occur.

**Acquired immune response**: see **adaptive immune response**.

Immunization with antigen is called **active immunization** to distinguish it from the transfer of antibody to an unimmunized individual, which is called passive immunization.

**Acute lymphoblastic leukemia** is a highly aggressive, undifferentiated form of lymphoid malignancy derived from a progenitor cell that is thought to be able to give rise to both lineages of lymphoid cells.

**Acute-phase proteins** are a series of proteins found in the blood shortly after the onset of an infection. These proteins participate in early phases of host defense against infection. An example is the mannose-binding protein.

The **acute-phase response** is a change in the blood that occurs during early phases of an infection. It includes the production of acute-phase proteins and also of cellular elements.

The **adaptive immune response** or **adaptive immunity** is the response of antigen-specific lymphocytes to antigen, including the development of immunological memory. Adaptive immune responses are generated by clonal selection of lymphocytes. Adaptive immune responses are distinct from innate and non-adaptive phases of immunity, which are not mediated by clonal selection of antigen-specific lymphocytes. Adaptive immune responses are also known as **acquired immune responses**.

The **adaptor proteins** are key linkers between receptors and downstream members of signalling pathways. These proteins are functionally heterogeneous, but share an SH2 domain as the means of interacting with the phoshotyrosine residues g nerated by the receptor-associated tyrosine kinases. Th protein kn wn as **Vav** is an adaptor protein of this type.

The **adenoids** are **mucosal-associated lymphoid tissues** located in the nasal cavity.

The enzyme defect **adenosine deaminase deficiency** leads to the accumulation of toxic purine nucleosides and nucleotides, resulting in the death of most developing lymphocytes within the thymus. It is a common cause of severe combined immunodeficiency.

**Adhesion molecules** mediate the binding of one cell to other cells or to extracellular matrix proteins. Integrins, selectins, members of the immunoglobulin gene superfamily, and CD44 and related proteins are all adhesion molecules important in the operation of the immun system.

An **adjuvant** is any substance that enhances the immune response to an antigen with which it is mixed.

**Adoptive immunity** is immunity conferred on a naive or irradiated recipient by transfer of lymphoid cells from an actively immunized donor. This is called **adoptive transfer** or **adoptive immunizati n**.

**Afferent lymphatic vessels** drain fluid from the tissues and carry antigens from sites of infection in most parts of the body to the lymph nodes.

**Affinity** is the strength of binding of one molecule to another at a single site, such as the binding of a monovalent Fab fragment of antibody to a monovalent antigen. See also **avidity**.

**Affinity chromatography** is the purification of a substance by means of its affinity for another substance immobilized on a solid support; an antigen can be purified by affinity chromatography on a column of specific antibody molecules covalently linked to beads.

**Affinity maturation** refers to the increase in the affinity of the antibodies produced during the course of a humoral immune response. It is particularly prominent in secondary and subsequent immunizations.

**Agammaglobulinemia**: see **X-linked agammaglobulinemia**.

**Agglutination** is the clumping together of particles, usually by antibody molecules binding to antigens on the surfaces of adjacent particles. Such particles are said to **agglutinate**. When the particles are red blood cells, the phenomenon is called hemagglutinati n.

**Agonist peptides** are peptide antigens that activate their specific T cells, inducing them to make cytokines and to proliferate.

**AIDS**: see **acquired immune deficiency syndrome**.

**Alleles** are variants of a single genetic locus.

**Allelic exclusion** refers to the fact that in a heterozygous individual, only one of the alternative C-region alleles of the heavy or light chain is expressed in an immunogl bulin molecule. The term has come to be used mor generally to describ the expression of a single receptor specificity in cells with the potential t express two or more receptors.

**Allergens** are antigens that elicit hyp rsensitivity or allergic reactions.

**Allergic asthma** is constriction of the bronchial tree due to an allergic reaction to inhaled antigen.

An **allergic reaction** is a response to innocuous environmental antigens or allergens due to pre-existing antibody or T cells. There are various immune mechanisms of allergic reactions, but the most common is the binding of allergen to IgE antibody on mast cells that causes asthma, hay fever, and other common allergic reactions.

**Allergic rhinitis** is an allergic reaction in the nasal mucosa, also known as hay fever, that causes runny nose, sneezing and tears.

**Allergy** is the symptomatic reaction to a normally innocuous environmental antigen. It results from the interaction between the antigen and the antibody or T cells produced by earlier exposure to the same antigen.

Two individuals or two mouse strains that differ at the MHC are said to be **allogeneic**. The term can also be used for allelic differences at other loci. See also **syngeneic**; **xenogeneic**.

Rejection of grafted tissues from unrelated donors usually results from T-cell responses to **allogeneic** MHC molecules expressed by the grafted tissues.

An **allograft** is a graft of tissue from an allogeneic or non-self donor of the same species; such grafts are invariably rejected unless the recipient is immunosuppressed.

**Alloreactivity** describes the stimulation of T cells by MHC molecules other than self; it marks the recognition of allogeneic MHC.

**Allotypes** are allelic polymorphisms that can be detected by antibodies specific for the polymorphic gene products; in immunology, **allotypic** differences in immunoglobulin molecules were important in deciphering the genetics of antibodies.

An **altered peptide ligand** is a peptide, usually closely related to an agonist peptide in amino acid sequence, that induces only a partial response from T cells specific for the agonist peptide.

The **alternative pathway** of complement activation is not triggered by antibody, as is the classical pathway of complement activation, but by the binding of complement protein C3b to the surface of a pathogen; it is therefore a feature of innate immunity. The alternative pathway also amplifies the classical pathway of complement activation.

**Anaphylactic shock** or systemic anaphylaxis is an allergic reaction to systemically administered antigen that causes circulatory collapse and suffocation due to tracheal swelling. It results from binding of antigen to IgE antibody on connective tissue mast cells throughout the body, leading to the disseminated release of inflammatory mediators.

**Anaphylatoxins** are small fragments of complement proteins released by cleavage during complement activation, that recruit fluid and inflammatory cells to sites of antigen deposition. The fragments C5a, C3a, and C4a are all anaphylatoxins, listed in order of decreasing potency *in vivo*.

Peptide fragments of antigens are bound to specific MHC class I molecules by **anchor residues**, which are amino acid side chains of the peptide that bind into pockets lining the peptide-binding groove of the MHC class I molecule. Each MHC class I molecule binds different patterns of anchor residues, each called an anchor motif, giving some specificity to peptide binding. Anchor residues are less obvious for peptides that bind to MHC class II molecules.

**Anergy** is a state of non-responsiveness to antigen. People are said to be anergic when they cannot mount delayed-type hypersensitivity reactions to challenge antigens, whereas T and B cells are said to be anergic when they cannot respond to their specific antigen under optimal conditions of stimulation.

**Antagonist peptides** are peptides, usually closely related in sequence to an agonist peptide, that inhibit the response of a cloned T-cell line specific for the agonist peptide.

An **antibody** is a protein that binds specifically to a particular substance—its antigen. Each antibody molecule has a unique structure that enables it to bind specifically to its corresponding antigen, but all antibodies have the same overall structure and are known collectively as immunoglobulins. Antibodies are produced by plasma cells in response to infection or immunization, and bind to and neutralize pathogens or prepare them for uptake and destruction by phagocytes.

**Antibody-dependent cell-mediated cytotoxicity (ADCC)** is the killing of antibody-coated target cells by cells with Fc receptors that recognize the Fc region of the bound antibody. Most ADCC is mediated by NK cells that have the Fc receptor FcγRIII or CD16 on their surface.

The **antibody repertoire** describes the total variety of antibodies that an individual can make.

An **antigen** is any molecule that can bind specifically to an antibody. Their name arises from their ability to **gen**erate **ant**ibodies. However, some antigens do not, by themselves, elicit antibody production; those antigens that can induce antibody production are called immunogens.

**Antigen:antibody complexes** are non-covalently associated groups of antigen and antibody molecules which can vary in size from small, soluble complexes to large, insoluble complexes that precipitate out of solution; they are also known as immune complexes.

The **antigen-binding site** of an antibody is the surface of the antibody molecule that makes physical contact with the antigen. Antigen-binding sites are made up of six hypervariable loops, three from the light-chain V region and three from the heavy-chain V region.

T and B lymphocytes collectively bear on their surface highly diverse **antigen receptors** capable of recognizing a wide diversity of antigens. Each individual lymphocyte bears receptors of a single antigen specificity.

An **antigenic determinant** is the portion of an antigenic molecule that is bound by a given antibody; it is also known as an epitope.

Influenza virus varies from year to year by a process of **antigenic drift** in which point mutations of viral genes cause small differences in the structure of viral surface antigens. Periodically, influenza viruses undergo an **antigenic shift** through reassortment of their segmented genome with another influenza virus, changing their surface antigens radically. Such antigenic shift variants are not recognized by individuals immune to influenza, so when antigenic shift variants arise, there is widespread and serious disease.

Many pathogens evade the adaptive immune response by **antigenic variation** in which new antigens are displayed that are not recognized by antibodies or T cells elicited in earlier infections.

**Antigen presentation** describes the display of antigen as peptide fragments bound to MHC molecules on the surface of a cell; all T cells recognize antigen only when it is presented in this way.

**Antigen-presenting cells** are highly specialized cells that can process antigens and display their peptide fragments on the cell surface together with molecules required for lymphocyte activation. The main antigen-presenting cells for T cells are dendritic cells, macrophages, and B cells, whereas the main antigen-presenting cells for B cells are follicular dendritic cells.

**Antigen processing** is the degradation of proteins into peptides that can bind to MHC molecules for presentation to T cells. All antigens except peptides must be processed into peptides before they can be presented by MHC molecules.

**Anti-immunoglobulin antibodies** are antibodies against immunoglobulin constant domains, useful for detecting bound antibody molecules in immunoassays and other applications.

**Hematopoiesis** is the generation of the cellular elements of blood, including the red blood cells, leukocytes and platelets. These cells all originate from pluripotent **hematopoietic stem cells** whose differentiated progeny divide under the influenc of **hemat poietic growth fact rs**.

A **hematopoietic lineage** is any developmental series of cells that derives from hematopoietic stem cells and results in the production of mature blood cells.

**Hemolytic disease of the newborn**, or erythroblastosis fetalis, is caused by a maternal IgG antibody response to paternal antigens expressed on fetal red blood cells. The usual target of this response is the Rh blood group antigen. The maternal anti-Rh IgG antibodies cross the placenta to attack the fetal red blood cells.

The **hemolytic plaque assay** detects antibody-forming cells by the ability of their secreted antibodies to produce a **hemolytic plaque**, an area of localized destruction of a thin layer of red blood cells around each antibody-producing cell. The antibodies secreted by the B cell are trapped by antigens on the red blood cells immediately surrounding it, and then complement is added that is triggered by the bound antibody to lyse the red blood cells.

Recombination signal sequences (RSS) flanking gene segments consist of a seven-nucleotide **heptamer** and a nine-nucleotide nonamer of conserved sequence, separated by 12 or 23 nucleotides. RSSs form the target for the site-specific recombinase that joins the gene segments.

**Hereditary angioneurotic edema** is the clinical name for a genetic deficiency of the C1 inhibitor of the complement system. In the absence of C1 inhibitor, spontaneous activation of the complement system can cause diffuse fluid leakage from blood vessels, the most serious consequence of which is epiglottal swelling leading to suffocation.

Individuals **heterozygous** for a particular gene have two different alleles of that gene.

An excellent model for membranous glomerulonephritis is **Heymann's nephritis**, a disease induced by injecting animals with tubular epithelial tissue.

**High endothelial venules** (**HEV**) are specialized venules found in lymphoid tissues. Lymphocytes migrate from blood into lymphoid tissues by attaching to and migrating across the **high endothelial cells** of these vessels.

Tolerance to injected protein antigens occurs at low or high doses of antigen. Tolerance induced by the injection of high doses of antigen is called **high-zone tolerance**, whereas tolerance produced with low doses of antigen is called low-zone tolerance.

The **hinge region** of antibody molecules is a flexible domain that joins the Fab arms to the Fc piece. The flexibility of the hinge region in IgG and IgA molecules allows the Fab arms to adopt a wide range of angles, permitting binding to epitopes spaced variable distances apart.

**Histamine** is a vasoactive amine stored in mast cell granules. Histamine released by antigen binding to IgE molecules on mast cells causes dilation of local blood vessels and smooth muscle contraction, producing some of the symptoms of immediate hypersensitivity reactions. Anti-histamines are drugs that counter histamine action.

**Histocompatibility** is literally the ability of tissues (Greek: *histo*) to get along with each oth r. It is used in immunology to describe the genetic systems that determine the rejection of tissue and organ grafts resulting from immunological recognition of histocompatibility (H) antigens.

**HIV**: see **human immunodeficiency virus**.

**HLA**, the acronym for **H**uman **L**eukocyte **A**ntigen, is th genetic designation for the human MHC. Individual loci are designated by upper-case letters, as in HLA-A, and all les are designated by numbers, as in HLA-A*0201.

The invariant **HLA-DM** molecul in humans is involved in loading peptides onto MHC class II molecules. It is encoded in the MHC within a set of genes resembling MHC class II genes. A hom logous protein in mice is called H-2M.

**Hodgkin's disease** is a malignant disease in which antigen-presenting cells that resemble dendritic cells seem to be th transformed cell type. **Hodgkin's lymphoma** is a form of Hodgkin's disease in which lymphocytes predominate, and it has a much better prognosis than the nodular sclerosis form of this disease in which th predominant cell type is non-lymphoid.

**Homeostasis** is a generic term describing the status of physiological normality. In the case of lymphocytes, homeostasis refers to an uninfected individual who has normal numbers of lymphocytes.

Cellular genes can be disrupted by **homologous recombination** with copies of the gene into which erroneous sequences hav been inserted. When these exogenous DNA fragments are introduced into cells, they recombine selectively with the cellular gene through remaining regions of sequence homology, replacing the functional gene with a non-functional copy.

The **human immunodeficiency virus** (**HIV**) is the causative agent of the acquired immune deficiency syndrome (AIDS). HIV is a retrovirus of the lentivirus family that selectively infects CD4 T cells, leading to their slow depletion, which eventually results in immunodeficiency.

**Humanization** is a term used to describe the genetic engineering of mouse hypervariable loops of a desired specificity into otherwise human antibodies. The DNA encoding hypervariabl loops of mouse monoclonal antibodies or V regions selected in phage display libraries is inserted into the framework regions of human immunoglobulin genes. This allows the production of antibodies of a desired specificity that do not cause an immune response in humans treated with them.

**Humoral immunity** is the antibody-mediated specific immunity made in a **humoral immune response**. Humoral immunity can be transferred to unimmunized recipients by using immune s rum containing specific antibody.

Monoclonal antibodies are most commonly produced from **hybridomas**. These are hybrid cell lines formed by fusing a specific antibody-producing B lymphocyte with a myeloma cell that is selected for its ability to grow in tissue culture and an abs nce of immunoglobulin chain synthesis.

**Hyperacute graft rejection** of an allogenic tissue graft is an immediate reaction caused by natural preformed antibodies that react against antigens on the graft. The antibodies bind to endothelium and trigger the blood clotting cascade, leading to an eng rged, ischemic graft and rapid loss of the organ.

Repetitive immunization to achieve a heightened state of immunity is called **hyperimmunization**.

Immune responses to innocuous antigens that lead to symptomatic reactions upon re-exposure are called **hypersensitivity reactions**. These can cause **hypersensitivity diseases** if th y occur repetitively. This state of heightened reactivity to antigen is called **hypersensitivity**. Hypersensitivity reactions are classified by mechanism: type I hypersensitivity reactions involve IgE antibody triggering of mast cells; type II hypersensitivity reactions involve IgG antibodies against cell-surface or matrix antigens; type III hypersensitivity reactions involve antigen:antibody complexes; and type IV hypersensitivity reactions are T-cell mediated.

The **hypervariabl (HV) regi ns** of immunoglobulin and T-cell receptor V domains are small regions that make contact with the antigen and differ extensively from one receptor to the next. Cf. **framework regions**.

**ICAM**: see **intercellular adhesion molecule**.

**Iccosomes** are small fragments of membrane coated with immune complexes that fragment off th processes of follicular dendritic cells

**in•fan•try•man** in'[illegible]-mən. A soldier in the infantry.
**infant school** *n. Chiefly British.* A kindergarten.
**in•farct** (in'färkt', in-färkt') *n. Pathol.* An area of tissue that undergoes necrosis as a result of obstruction of local blood supply. [< Lat. *infarctus*, p.part. of *infarcire*, to cram : *in-*, in; see IN-[2] + *farcire*, to stuff.] — **in•farct'ed** *adj.*
**in•farc•tion** (in-färk'shən) *n.* 1. The formation or development of an infarct. 2. An infarct.
**in•fat•u•ate** (in-fach'ōō-āt') *tr.v.* **-at•ed, -at•ing, -ates.** 1. To inspire with unreasoning love or attachment. 2. To cause to behave foolishly. — *adj.* (-it, -āt'). Infatuated. [Lat. *infatuāre, infatuāt-* : *in-*, causative pref.; see IN-[2] + *fatuus*, foolish.]
**in•fat•u•at•ed** (in-fach'ōō-ā'tid) *adj.* Possessed by an unreasoning passion or attraction. — **in•fat'u•at'ed•ly** *adv.*
**in•fat•u•a•tion** (i-fach'ōō-ā'shən) *n.* 1. A foolish, unreasoning, or extravagant passion or attraction. See Syns at **love.** 2. An object of extravagant, short-lived passion.
**in•fau•na** (in'fô'nə) *n.* Aquatic animals that live in the substrate of a body of water. [IN-[2] + FAUNA.]
**in•fea•si•ble** (in-fē'zə-bəl) *adj.* Not feasible; impracticable.
**in•fect** (in-fekt') *tr.v.* **-fect•ed, -fect•ing, -fects.** 1. To contaminate with a pathogen. 2. To communicate a pathogen or disease to. 3. To invade and produce infection in. 4. To contaminate or corrupt. 5. To affect in a contagious way. [ME *infecten*, to afflict with disease < Lat. *inficere, infect-*, to stain, infect : *in-*, in; see IN-[1] + *facere*, to do; see **dhē-**[1].]
**in•fec•tion** (in-fek'shən) *n.* 1.a. Invasion by and multiplication of pathogenic microorganisms in a body tissue. b. An instance of being infected. c. An agent or a contaminated substance responsible for one's becoming infected. d. The pathological state resulting from having been infected. 2. An infectious disease. 3.a. Moral contamination or corruption. b. Ready communication of an emotion or attitude by contact or example.
**in•fec•tious** (in-fek'shəs) *adj.* 1. Capable of causing infection. 2. Caused by or capable of being transmitted by infection. 3. Easily or readily communicated: *an infectious laugh.* — **in•fec'tious•ly** *adv.* — **in•fec'tious•ness** *n.*
**infectious enterohepatitis** *n.* See **blackhead** 2.
**infectious hepatitis** *n.* See **hepatitis A.**
**infectious mononucleosis** *n.* An acute infectious disease caused by Epstein-Barr virus and characterized by fever, swollen lymph nodes, sore throat, and lymphocyte abnormalities.
**in•fec•tive** (in-fek'tiv) *adj.* Capable of producing infection; infectious. — **in•fec'tive•ness, in'fec•tiv'i•ty** *n.*
**in•fe•lic•i•tous** (in'fi-lis'i-təs) *adj.* 1. Inappropriate; ill-chosen: *an infelicitous remark.* 2. Not happy; unfortunate.
**in•fe•lic•i•ty** (in'fi-lis'i-tē) *n., pl.* **-ties.** 1. The quality or condition of being infelicitous. 2. Something inappropriate or unpleasing. [ME *infelicite* < Lat. *infēlicitās* < *infēlix, infēlic-*, unhappy : *in-*, not; see IN-[1] + *fēlix*, happy; see **dhē(i)-**[1].]
**in•fer** (in-fûr') *v.* **-ferred, -fer•ring, -fers.** — *tr.* 1. To conclude from evidence or premises. 2. To reason from circumstance; surmise. 3. To lead to as a consequence or conclusion: *"Socrates argued that a statue inferred the existence of a sculptor"* (Academy). 4. *Usage Problem.* To hint; imply. — *intr.* To draw inferences. [Lat. *inferre*, to bring in, adduce : *in-*, in; see IN-[2] + *ferre*, to bear; see **bher-**[1]*.] — **in•fer'a•ble** *adj.* — **in•fer'a•bly** *adv.* — **in•fer'rer** *n.*

***Usage Note:*** The traditional distinction between *imply* and *infer* is a useful one. When we say that a speaker or sentence implies something, we mean that it is conveyed or suggested without being stated outright: *When the mayor said that she would not rule out a business tax increase, she implied* (not *inferred*) *that some taxes might be raised.* Inference, on the other hand, is the activity performed by a reader or interpreter in deriving conclusions that are not explicit in what is said: *When the mayor said that she would not rule out a tax increase, we inferred that she had been consulting with some new financial advisers, since her old advisers were in favor of tax reductions.*

**in•fer•ence** (in'fər-əns) *n.* 1.a. The act or process of deriving logical conclusions from premises known or assumed to be true. b. The act of reasoning from factual knowledge or evidence. 2.a. Something inferred. b. *Usage Problem.* A hint or suggestion. See Usage Note at **infer.**
**in•fer•en•tial** (in'fə-rən'shəl) *adj.* 1. Of, relating to, or involving inference. 2. Derived or capable of being derived by inference. — **in'fer•en'tial•ly** *adv.*
**in•fe•ri•or** (in-tir'ē-ər) *adj.* 1. Low or lower in order, degree, or rank. 2.a. Low or lower in quality, value, or estimation: *felt inferior to his older sibling.* b. Second-rate; poor. 3. Situated under or beneath. 4. *Bot.* Located below the perianth and other floral parts. Used of an ovary. 5. *Anat.* Located beneath or directed downward. 6. *Print.* Set below the normal line of type; subscript. 7. *Astron.* a. Orbiting between the earth and the sun. b. Lying below the horizon. — *n.* 1. A person lower in rank, status, or accomplishment than another. 2. *Print.* An inferior character, such as the number 2 in $CO_2$. [ME < Lat. *inferior*, comp. of *inferus*, low. See **ndher-**[1]*.] — **in•fe'ri•or'i•ty** (-ôr'i-tē, -ŏr'-) *n.*
**inferiority complex** *n.* A persistent tendency to self-diminishment.
**in•fer•nal** (in-fûr'nəl) *adj.* 1.a. Of o of the dead. b. Of or relating to he *infernal instruments of war.* 3. At OFr. < LLat. *infernālis* < *inferna* derground. See **ndher-**[1]*.] — **in•fer**
**infernal machine** *n. Law.* An explo signed to harm or destroy.
**in•fer•no** (in-fûr'nō) *n., pl.* **-nos.** 1. gestive of hell. 2. A place of fiery hell < LLat. *infernus*. See INFERNAL.
**in•fer•tile** (in-fûr'tl) *adj.* 1. Not fe ren. 2. *Biol.* Incapable of producir
**in•fer•til•i•ty** (in'fər-til'i-tē) *n.* 1. tility. 2. The persistent inability to
**in•fest** (in-fest') *tr.v.* **-fest•ed, -fest** or overrun in numbers large enoug ing, or obnoxious. 2. To live as a *infested with tapeworms.* [ME *in infester* < Lat. *infestāre* < *infesta* — **in'fes•ta'tion** *n.* — **in•fest'er**
**in•fi•del** (in'fi-dəl, -dēl') *n.* 1. An a particular religion, esp. Christia has no religious beliefs. 3. One wi ticular doctrine, system, or princip Lat. *infidēlis*, disloyal : *in-*, not; se *fidēs*, faith; see **bheidh-**[1]*.]
**in•fi•del•i•ty** (in'fi-dēl'i-tē) *n., pl* to a sexual partner, esp. a spous faithfulness. 2. Lack of loyalty. 3.
**in•field** (in'fēld') *n.* 1. *Baseball.* bounded by home plate and first b. The defensive positions of firs base, and shortstop considered as inside a racetrack or running trac farmhouse.
**in•field•er** (in'fēl'dər) *n. Baseball.*
**in•fight•ing** (in'fī'ting) *n.* 1. Cont ment among members or group 2. *Sports.* Fighting or boxing at cl
**in•fil•trate** (in-fil'trāt', in'fil- **-trates.** — *tr.* 1.a. To pass (troops, ly into enemy-held territory. b. T tent. 2. To enter or take up posit titiously, as for espionage. 3. To c to permeate by passing through permeate (a porous substance) wit gain entrance gradually or surrep filtrates, esp. an abnormal substa ually in cells or body tissues. — **i** — **in•fil'tra•tor** *n.*
**in•fil•tra•tion** (in'fil-trā'shən) *n.* infiltrating. 2. The state of being i infiltrates.
**infin.** *abbr.* Infinitive.
**in•fi•nite** (in'fə-nit) *adj.* 1. Havin 2. Immeasurably great or large tance. 3. *Math.* a. Existing beyon arbitrarily large value. b. Unlimit relating to a set capable of being spondence with a proper subset o finite. — **in'fi•nite•ly** *adv.* — **in'**

***Syns:*** *infinite, boundless, etern* The central meaning shared by th beginning or end": *infinite wisdom nal beauty; illimitable space; eter* at **incalculable.** ***Ant:*** *finite.*

***Usage Note:*** *Infinite* is some terms such as *unique, absolute,* strict mathematical sense it allow comparison; one quantity cannot other. Unlike other absolute term not permit modification by adver In nontechnical usage *infinite* is refer to an unimaginably large de comparison of the word is uncer at **unique.**

**in•fin•i•tes•i•mal** (in'fin-i-tes'ə or incalculably minute. 2. *Math* approaching zero as a limit. — or quantity. 2. *Math.* An infinitesi NLat. *infinitēsimus*, infinite in ord See INFINITE.] — **in'fin•i•tes'i•mal**
**infinitesimal calculus** *n. Math.* culus.
**in•fin•i•ti•val** (in'fin-i-tī'vəl) *adj.*
**in•fin•i•tive** (in-fin'i-tiv) *n.* A substantive while retaining certain that in English may be preceded too, or may also occur without See Usage Note at **split infinitive.**